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Effective antihypertensive treatment fails to control blood pressure during exercise

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Short title: Exercise blood pressure in controlled hypertension

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Abstract

An exaggerated blood pressure response to maximal exercise is an independent risk factor for cardiovascular events and mortality. It is unclear if treating blood pressure to guideline recommended levels could normalise the rise in blood pressure during exercise, which is mediated by the metaboreflex. We aimed to assess the blood pressure response to incremental exercise testing and metaboreflex activation in treated-controlled hypertension (n=16), treated-uncontrolled hypertension (n=16), and untreated-hypertension (n=11) and 16 control participants with normal blood pressure (n=16). All groups were matched for age and body mass index. Blood pressure was measured during an incremental VO_2 peak test on a cycle ergometer and during metaboreflex isolation using post-exercise ischemia. Data were analysed using two-way analysis of variance with Tukey test for multiple comparisons. Aerobic fitness was similar among groups ($P=0.97$). The rise in absolute systolic blood pressure from baseline at peak exercise was similar in controlled-, uncontrolled- and untreated hypertension but greater compared to normotensive controls ($\Delta 71 \pm 3$, 81 ± 7 , 79 ± 8.5 vs. 47 ± 5 mmHg, $P < 0.0001$). Metaboreflex sensitivity was also similar in controlled-, uncontrolled-, and untreated-hypertension but augmented compared to normotensive controls (Δ systolic blood pressure; 21 ± 2 , 28 ± 2 , 25 ± 3 vs. 12 ± 2 mmHg $P < 0.0001$). An amplified pressor response to exercise occurred in patients taking anti-hypertensive medication, despite having controlled blood pressure at rest and was potentially caused (in part) by enhanced metaboreflex sensitivity. Poor blood pressure control during exercise, partially mediated by the metaboreflex, may contribute to the heightened risk of an adverse cardiovascular event even in treated-controlled patients.

Key words: Hypertension, metaboreflex, exercise pressor reflex, exercise blood pressure.

Introduction

Chronic aerobic endurance training lowers resting blood pressure (BP) in patients with hypertension ¹. However, the *acute* rise in systolic BP (SBP) during both static and dynamic exercise, in patients with untreated or uncontrolled hypertension, is exaggerated compared to that observed in normotensive individuals ²⁻⁵. This is problematic as exaggerated increases in moderate and peak exercise SBP are associated with the risk of end organ damage (e.g. left ventricular hypertrophy) ^{6,7}, cardiovascular disease (fatal and non-fatal) ⁸⁻¹¹, stroke ^{10,12} and total mortality ^{11,13}.

Adjustments in the autonomic nervous system during exercise are mediated by feed-forward signals from the brain (central command ¹⁴) as well as group III (mechanoreflex ¹⁵) and group IV (metaboreflex ¹⁶) afferents that lie within the skeletal muscle (the exercise pressor reflex (EPR) ¹⁷). The mechanoreflex and metaboreflex are crucial for mediating the rise in sympathetic nerve activity (SNA) that occurs during exercise, which increases BP to augment skeletal muscle blood flow.

In patients with untreated hypertension the level of SNA is elevated at both rest ¹⁸ and during dynamic ¹⁹ and isometric ³ handgrip exercise. Since inhibition of the group III and IV muscle afferents, using intrathecal fentanyl, normalised the acute BP response to dynamic exercise in untreated hypertensives to levels attained in normotensive individuals, this demonstrated a major role of the EPR in controlling BP during exercise in this population ². Previous work in both animal models of hypertension ^{20,21} and humans ^{3-5,22} shows that the metaboreflex plays an important role in the exaggerated response of SNA and BP to exercise. Little information is

available regarding the effect of anti-hypertensive medication on the SBP response to exercise, and the sensitivity of the metaboreflex. Studies have examined the BP response to exercise and the role of the metaboreflex only in untreated hypertensives ² and mixed groups of hypertensives (untreated or withdrawn from anti-hypertensive medications ³⁻⁵). Although these studies have contributed to the knowledge base regarding the importance of exercise BP and the role of the metaboreflex, we do not know whether patients with treated-controlled hypertension have an exaggerated response to exercise and whether the metaboreflex remains hyperactive relative to age/sex matched normotensive controls. Exaggerated exercise BP was associated with depressed regression of left ventricular hypertrophy in patients with controlled hypertension, but no comparisons were made to normotensive controls⁷. This is important because despite treating BP to recommended levels, some studies show that patients with controlled BP at rest have an elevated risk of cardiovascular disease ^{23,24}, all-cause mortality ^{23,25} and stroke ²⁴ compared to normotensive controls. To explain this, we proposed that current anti-hypertensive medications do not act on the known mechanisms that sensitize the metaboreflex in hypertension (e.g. acid-sensing ion channels (ASIC), purinergic receptors (P2X) and transient receptor potential of the vanilloid type 1 (TRPV1) ^{26,27}) and thus cannot prevent the exaggerated spikes in BP during exercise. Thus, we hypothesised that the rise in BP during peak cardiopulmonary exercise and specific metaboreflex testing will be exaggerated in patients with controlled- and uncontrolled hypertension (similar to patients with untreated hypertension) compared to normotensive participants.

Methods

The analytic methods and summary data tables that support the findings of this study are available from the authors on request.

Participants

We recruited 59 participants; 16 normotensives, 16 treated-uncontrolled, 16-treated-controlled and 11 untreated hypertensives, matched for age, body mass index (BMI) and cardiovascular fitness (as measured by a volume of oxygen inspired (VO₂) peak test). This study was approved by Southwest-Exeter NHS REC (16/SW/0004) and local Research and Development (R&D) approval. All participants provided their written informed consent prior to participation. Participant demographics are shown in Table 1. 29 of the participants (49%) were female and 27 (93%) of these were postmenopausal. Participants attended the Clinical Research and Imaging Centre-Bristol at the same time of day and the lab conditions were at a set temperature (22°C). All participants were asked to abstain from intense exercise 24-hours before the study. All experimental protocols conformed to the Declaration of Helsinki. See online supplements for inclusion and exclusion criteria (please see <http://hyper.ahajournals.org>).

Study design

This was a case-control study. Investigators were blinded during analysis of data.

Screening procedure

See online supplement for BP and other screening procedures (please see <http://hyper.ahajournals.org>).

VO₂ peak testing

VO₂ peak was assessed by an incremental exercise test on an upright cycle ergometer (Love Medical, Manchester, UK). See online supplementary methods for the specific incremental exercise protocol (please see <http://hyper.ahajournals.org>).

The Metaboreflex

Post-exercise ischemia

The metaboreflex was assessed using post-exercise ischemia (PEI) following 1 minute of isometric handgrip exercise at 30% maximal voluntary contraction (MVC) (please see <http://hyper.ahajournals.org> for online supplement). PEI is the standard protocol to assess metaboreflex sensitivity in humans ^{16,28}. Following isometric handgrip exercise an occlusion cuff was inflated on the arm that performed the handgrip exercise to suprasystolic pressures (>240 mmHg) to isolate the metaboreflex; this is the PEI period. The occlusion cuff remained inflated at suprasystolic pressures for 1.5 minutes during PEI ^{3,4}. The period following exercise where the occlusion cuff remains inflated represents PEI and isolation of the metaboreflex ^{3-5,16}. The BP and heart rate (HR) response during PEI was used as the assessment of the metaboreflex response to exercise.

Physiological monitoring during exercise

BP was measured every 1.5 minutes during VO₂ peak testing using an automated sphygmomanometer (manufactured specifically for exercise BP monitoring; Love Medical, Manchester, UK) on the left arm of the participant. A 12-lead electrocardiogram (ECG) (Love Medical, Manchester, UK) was used to measure HR during the VO₂ peak test.

During static handgrip exercise and PEI the change in arterial BP was measured on a beat-to-beat basis using finger plethysmography (Finometer, FMS, Netherlands) and the change in HR was recorded using a 3-lead ECG. During static handgrip exercise and PEI, all data were collected on a data acquisition system (LabChart 7, AD instruments).

Data analysis

See online supplement for data analysis (please see <http://hyper.ahajournals.org>).

Statistics

Participant characteristics were compared using a one-way analysis of variance (one-way ANOVA), with a Tukey test for multiple comparisons. Group averages (normotension, treated-controlled, treated-uncontrolled and untreated hypertension) of SBP, diastolic BP (DBP), mean arterial pressure (MAP) and HR during the VO₂ peak test were compared using a two-way analysis of variance (two-way ANOVA), with a Tukey test for multiple comparisons.

The handgrip and PEI period were broken down in to 30 second periods (0-30s handgrip, 30-60s handgrip, PEI 1 (60-90s), 2 (90-120s) and 3 (120-150s) and the group averages were compared using an ordinary two-way ANOVA., with a Tukey test for multiple comparisons. Data are reported as mean +/- standard error. The α -level was set at 0.05.

Results

Participant demographics

All participants were matched for age ($P=0.73$), BMI ($P=0.25$) and cardiovascular fitness (VO_2 peak) ($P>0.97$) (see Table 1 and Table S1; please see <http://hyper.ahajournals.org>). There was a difference in daytime ambulatory SBP between groups ($F=26.57$, $P<0.0001$). A Tukey post hoc showed that people with treated-uncontrolled hypertension (145 ± 3 mmHg) had higher daytime ambulatory SBP compared to treated-controlled hypertensives (125 ± 2 mmHg; $P<0.0001$) and normotensives (120 ± 2 mmHg; $P<0.0001$). Untreated hypertensive patients had similar daytime ambulatory SBP when compared to the treated-uncontrolled group (145 ± 3 vs. 145 ± 3 mmHg respectively; $P=0.99$) but higher than treated-controlled hypertensives (125 ± 2 mmHg; $P<0.0001$) and normotensives (120 ± 2 ; $P<0.0001$). Importantly, treated controlled hypertensives had a similar SBP to normotensive controls (125 ± 2 vs. 120 ± 2 mmHg; $P=0.37$). Similar results were found in daytime ambulatory DBP (please see <http://hyper.ahajournals.org> for the online supplement for results regarding ambulatory DBP and HR). Anti-hypertensive medication is shown in Table 1. No participants had received device or surgical interventions to treat their hypertension.

VO₂ peak test

There was an interaction between group and % of VO_2 peak on the change in SBP ($F(15,330) = 2.86$, $P=0.0003$). The Tukey post-hoc test showed that the absolute *increase* in SBP from baseline during low intensity exercise (0-25, 26-50% VO_2 peak) was similar between all groups ($P>0.05$; Figure 1a). However, during moderate-high intensity exercise (51-75% VO_2 peak) the treated-uncontrolled and the treated-controlled hypertensive group had comparable exaggerated increases in absolute SBP that were larger compared to normotensive controls ($P=0.008$ and $P=0.046$).

respectively; Figure 1a). Similarly, at peak exercise treated-controlled, treated-uncontrolled and untreated hypertensives had a comparable increase in SBP that were greater compared to normotensive controls ($P<0.0001$, $P<0.0001$ and $P<0.0001$ respectively; Figure 1a). We also found similar results when assessing the absolute SBP and % change in SBP measured at each progressive exercise intensity (Figure S1A and S2A; please see <http://hyper.ahajournals.org> for the online supplement). The absolute SBP change per minute of VO_2 peak test ($\Delta\text{SBP}/\text{min}$) was significantly different between groups ($F=5.762$, $P=0.0017$). The increase in absolute SBP per minute of the VO_2 peak test ($\Delta\text{SBP}/\text{min}$) was similar in treated-controlled, treated-uncontrolled and untreated hypertension but higher than in normotensive controls ($8\pm 1, 8\pm 1, 8\pm 1$ vs. 5 ± 0 mmHg respectively; $P=0.0190$, $P=0.002$ and $P=0.023$ respectively).

The DBP response to exercise was similar to the results found for SBP and can be found in the online supplement (please see <http://hyper.ahajournals.org>).

There was an interaction between the groups and % of VO_2 peak on the change in HR ($F(15,275) = 2.032$, $P = 0.014$). The rise in HR from baseline was similar between all groups up to 76-100% VO_2 peak; at peak exercise untreated hypertensives had an exaggerated rise in absolute HR compared to treated-uncontrolled hypertensives ($P=0.047$; Figure 1d). At peak VO_2 , untreated hypertensives had a greater increase in absolute HR compared to normotensive controls and treated-uncontrolled hypertensives ($P=0.011$ and $P=0.001$; Figure 1d). Additionally, the rise in absolute HR was greater in the treated-controlled hypertensives compared to that measured in the treated-uncontrolled hypertension group and the normotensive controls at peak VO_2

($P=0.003$ and $P=0.037$; Figure 1d). Similar results were found at peak exercise (Figure 1d). For respiratory data during the VO_2 peak test, please see the online supplementary material (<http://hyper.ahajournals.org>).

Handgrip exercise

For results pertaining to data sampled during the isometric handgrip test, please see the online supplementary material (<http://hyper.ahajournals.org>).

Metaboreflex

Two treated-controlled hypertensive participants withdrew from the study following visit one, therefore, 14 treated-controlled hypertensives have completed metaboreflex testing. There was an interaction between the groups and time on the change in SBP during metaboreflex activation using PEI ($F(15,265) = 4.222$, $P < 0.0001$). The absolute increase in SBP, DBP, MAP and HR from baseline across all time points (isometric handgrip and PEI; 30s averages) are displayed in Figure 2a-d. The Tukey multiple comparisons post hoc test showed that the increase in SBP from baseline during all 30s epochs of PEI was similar between the treated-controlled, treated-uncontrolled group and untreated hypertensive groups ($P \geq 0.05$).

The treated-controlled, treated-uncontrolled and untreated hypertensive groups had a larger change in SBP compared to normotensive controls during PEI1 ($P < 0.0001$, $P=0.087$ and $P=0.0004$), PEI2 ($P < 0.0001$, $P=0.042$ and $P=0.0002$) and PEI3 ($P < 0.0001$, $P=0.0162$ and $P=0.0003$) (Figure 2a). An example of an individual SBP response to both isometric handgrip exercise and metaboreflex isolation can be found on Figure S4 (please see the online supplement, <http://hyper.ahajournals.org>).

There was an interaction between the groups and time on the change in DBP during PEI ($F(15,265) = 1.787, P = 0.036$). The rise in DBP in treated-controlled and treated-uncontrolled hypertensives remained similar during PEI ($P = 0.987$) but exaggerated when compared to that measured in normotensive controls during PEI1 ($P = 0.0186$ and $P = 0.0482$ respectively) and PEI2 ($P = 0.0252$ and $P = 0.0278$ respectively) (Figure 2b). During PEI3, only treated-controlled hypertensives had an exaggerated change in DBP compared to normotensives ($P = 0.032$). There were no group differences in HR response PEI ($F(15,260) = 1.306, P = 0.198$ respectively; Figure 2d).

Discussion

Our novel finding is that the increase in SBP during maximal exercise testing (VO_2 peak testing) is exaggerated in patients with treated-controlled hypertension (similar to that seen in treated-uncontrolled and untreated patients) compared to age; BMI and cardiovascular fitness (VO_2 peak) matched normotensive controls. Additionally, the change in SBP during metaboreflex isolation (PEI) was exaggerated in treated-controlled hypertension, similar to treated-uncontrolled and untreated hypertensives. We posit that the metaboreflex plays a role in driving this abnormal BP response to dynamic and static exercise in humans with treated and untreated hypertension. Given the inability of current antihypertensive medication to control BP during exercise, we are prompted to discuss fundamental changes in the clinical assessment and treatment of BP.

SBP responses to exercise and cardiovascular risk

The current goal of anti-hypertensive treatment is to lower resting BP, to achieve guideline recommended targets and reduce the risk of future adverse cardiovascular

events. BP responses to exercise are not usually considered despite the fact that exaggerated responses are predictive of end organ damage ^{6,7}, cardiovascular disease ^{8,9}, ischemic stroke ^{10,12}, acute myocardial infarction¹⁰ and total mortality ¹³. Our data indicate, for the first time, that an exaggerated BP response to exercise persists despite patients achieving guideline recommended BP targets with medication. This may explain why treated-controlled hypertensive patients have an elevated risk of cardiovascular events and mortality versus people with normotension ²³⁻²⁵. Potentially, exercise BP should be considered in routine BP assessment by clinicians. Said differently, measuring BP while resting in a chair will not fully reveal the cardiovascular risk of a patient.

The metaboreflex

Data from animals ^{20,21,29} and humans ³⁻⁵ show that the muscle metaboreflex is exaggerated in people with hypertension; we have confirmed these findings in humans. Previous research focusing on hypertension and the metaboreflex in humans has focused on untreated hypertensive patients ²² or a mixture of untreated hypertensive and treated hypertensives withdrawn from their medication ³⁻⁵. Our novel data indicate that in patients with treated-controlled hypertension the sensitivity of the metaboreflex is increased, contributing to the elevated BP response to exercise in this cohort. This is important because studies in hypertensive dogs showed that an exaggerated muscle metaboreflex caused coronary vasoconstriction during exercise, which limited the exercise induced increase in cardiac output ²⁹. Therefore, coronary perfusion during exercise could be impacted in hypertensive humans if metaboreflex sensitivity is high.

We did not find an exaggerated HR response to metaboreflex isolation, which is similar to previous findings using isometric handgrip exercise in human hypertension ^{3,4}. Typically, SNA responses to PEI, measured using microneurography (muscle SNA; MSNA) are exaggerated in hypertensive patients ^{3,5}. This has been confirmed in animal models of hypertension by measuring renal SNA during metaboreflex isolation ²⁰. Therefore, it is probable that increased MSNA responses to metaboreflex activation caused the increased BP in our patients. However, this was not directly measured.

The other component of the EPR, the mechanoreflex has also been shown to contribute to the exaggerated BP response to exercise in untreated hypertension ³⁰. We focused solely on the metaboreflex since previous data in untreated hypertension highlights its importance ^{3-5,22,31} and due to difficulties in isolating the mechanoreflex independent of the metaboreflex, central command and the arterial baroreflex during exercise.

Mechanisms

Exactly what drives the increased metaboreflex response to exercise in hypertension is unclear. It is probable that there is a supply and demand mismatch due to inadequate perfusion of the active vascular bed ^{19,32}. In healthy individuals, during exercise, the increased SNA directed towards the skeletal muscle is normally offset by locally produced vasodilatory metabolites (functional sympatholysis) ^{19,32}. In untreated hypertensives, functional sympatholysis is impaired, owing to altered nitric oxide signalling (in part due to endothelial damage and/or increased oxidative stress within the muscle ^{32,33}). This is combined with exaggerated SNA responses to exercise, leading to reductions in muscle perfusion and increased metabolites that

activate the metaboreflex ^{19,32,34}. Therefore, an impaired functional sympatholysis could also explain exaggerated metaboreflex sensitivity in treated-controlled hypertension. It could be postulated that standard first line anti-hypertensive medications (e.g. ACE inhibitors, angiotensin II receptor blockers (ARB), calcium channel blockers and/or thiazide like diuretic ³⁵) do not directly affect functional sympatholysis or metaboreflex sensitivity during exercise. However, this has not directly been assessed and requires future attention. For example, Irbesartan, an ARB, failed to improve functional sympatholysis or control of MSNA during dynamic handgrip exercise in untreated hypertensives ¹⁹. Other mechanisms could include alterations in the sensitivity/density of receptors sensitive to metabolites released during exercise, however, data supporting this concept is scant in hypertensives. The only study to date is by Mizuno et al ²⁰; the authors found that TRPV1 receptor expression is increased in the dorsal root ganglia of the spontaneously hypertensive rat, indicating potential upregulation of the receptor.

Given our findings of the inadequacies of antihypertensive drugs in controlling BP during exercise, any novel pharmacological interventions should consider reducing exercise SBP as well as resting BP. Potential targets could include chemically sensitive afferents and associated receptors in skeletal muscle. Since there are many receptors involved in the metaboreflex and much redundancy exists in humans ³⁶, blocking one receptor may not effectively reduce the exercise pressor response ^{5,20,36}. However, reducing metaboreflex sensitivity would be expected to reduce reflex increases in sympathetic vasoconstrictor activity to skeletal muscle and hence improve skeletal muscle blood flow. This would provide a way to reset metaboreflex sensitivity.

Putting the overt cardiovascular risk of acute exercise aside demonstrated herein, long term aerobic training (3-4 times per week) has improved functional sympatholysis in the femoral artery and subsequently the BP response to exercise of untreated hypertensive patients ³⁴. Improvement of long-term cardiovascular fitness could be an effective method for improving the autonomic response to exercise in treated and untreated hypertension. However, adherence to exercise regimes is typically poor, highlighting the need for improved strategies to promote exercise training and/or physical activity in the community ³⁷.

Study Limitations

There are several limitations. First, all the participants kept a 24-hour diary, which noted the times they took their medications; however, we cannot guarantee that treated-controlled and treated-uncontrolled hypertensives were taking their anti-hypertensive medication(s). Participants were asked to take their anti-hypertensive medication as normal on study days. Second, the treated-controlled patients began the study already treated for their hypertension and took a variety of different classes of medication, which may have had different effects on exercise BP ³⁸. Future studies should assess exercise BPs and metaboreflex sensitivity in treatment-naive hypertensives before and following effective anti-hypertensive treatment, assessing the effect of different types of anti-hypertensive medications. Third, PEI induced by circulatory occlusion can be perceived as painful for some participants. Patients who perceive a stimulus as more painful have an augmented BP response to the stimulus ³⁹. This could confound the BP response to PEI. We did not assess pain perception between groups, however, hypertensive patients have a blunted sensitivity to acute pain ³⁹. Forth, we measured the BP response to incremental dynamic exercise

because this is predictive of future cardiovascular morbidity but activated the metaboreflex using circulatory occlusion following static handgrip exercise. Future studies will need to activate the metaboreflex during exercise as the cardiovascular response to metaboreflex activation is different when activated during exercise compared to PEI ⁴⁰. It is also possible that anti-hypertensive medications alter the perception of effort of participants and in turn increase or decrease central command, which may have influenced the BP response to exercise ⁴¹. Finally, this was a single centre, case-controlled study which may limit its generalisability to other population groups. Comparing the BP response to metaboreflex activation following static exercise in a small muscle bed may not reflect how the metaboreflex is activated during dynamic exercise of a large muscle mass ⁴².

Perspectives

In the general population, Laukkanen et al. ¹⁰ found that individuals with a SBP rise of more than 64 mmHg at peak exercise are at most risk of an acute cardiovascular event ¹⁰. We found a comparable rise in SBP ($\Delta 72$ mmHg) in the treated-controlled hypertensive cohort in this study. Additionally, hypertensive patients who present an exaggerated BP response to exercise are more likely to have reduced improvement of left ventricular hypertrophy when compared to hypertensives with a normal BP response to exercise ⁷. However, Mizuno et al ⁷ did not include a control group with normal resting BP. Considering our findings, it is important that future research assesses the long-term prognosis of an exaggerated BP response to exercise in treated-controlled hypertensives. If these results are confirmed in larger multicentre studies, it would suggest the need for routine BP assessment during exercise in patients with hypertension (controlled, uncontrolled or untreated). Controlled BP at

rest but an exaggerated response to exercise may indicate an underlying cardiovascular pathology, which has not been treated by standard anti-hypertensive treatment. Measuring BP during exercise may help to identify those patients who are at increased risk of adverse cardiovascular outcomes. Our data support the need for developing new treatment strategies that attenuate the exercise pressor response, such targets might include ASIC, TPRV and/or P2X receptors ^{26,27}. Additionally, the SBP Intervention Trial (SPRINT) found that lowering SBP below 120 mmHg with intensive treatment resulted in fewer fatal and nonfatal cardiovascular events and death from any cause ⁴³. Lower BP targets in line with the SPRINT trial may reduce the SBP response to exercise and blunt the sensitivity of the metaboreflex. This may contribute to why lower BP targets confer added cardiovascular protection ⁴³.

Conclusion

This is the first study to show that the SBP responses to dynamic exercise (both submaximal and maximal) is augmented in patients with treated-controlled hypertension and is similar to that in patients with treated but uncontrolled and untreated hypertension. The exaggerated rise in SBP during moderate intensity exercise (i.e. at around 50% of VO₂ peak) may explain why this cohort are at greater risk of future cardiovascular events. The metaboreflex plays a key role in the exaggerated rise in SBP during exercise in treated and untreated hypertension and offers a new target for *dynamic* BP management.

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Conflicts of Interest/Disclosure Statement

None.

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Novelty and Significance

What Is New?

- The BP response to peak exercise is similar in treated and untreated hypertensives and augmented compared to normotensive individuals.
- The metaboreflex plays a part in regulating the exaggerated SBP response to peak exercise in treated and untreated hypertension.

What Is Relevant?

- Despite control of baseline BP, anti-hypertensive medication does not protect against exaggerated BP increases during peak exercise testing or metaboreflex testing.
- An exaggerated rise in blood pressure during exercise could place treated and untreated hypertensives at increased risk of adverse cardiovascular events compared to normotensives.

Summary

This is the first study to show that treated-controlled hypertensives, despite adequate control of baseline BP, have a similar BP response compared to treated-uncontrolled and untreated hypertension during peak dynamic exercise and metaboreflex testing.

Figure legends

Figure 1. The absolute change from baseline in A) Systolic blood pressure (SBP), B) diastolic blood pressure (DBP), C) Mean arterial pressure (MAP) and D) Heart rate (HR) during VO₂ peak testing. Changes in hemodynamics are calculated at different percentages of VO₂ peak and at peak exercise testing (VO₂ peak) to enable comparisons between groups. * $P < 0.05$ for all groups vs. normotension. † $P < 0.05$ uncontrolled hypertension vs. normotension. ‡ $P < 0.05$ controlled hypertension vs. normotension. § $P < 0.05$ controlled and uncontrolled hypertension vs. untreated hypertension. || $P < 0.05$ untreated hypertension vs. normotension. # $P < 0.05$ controlled hypertension vs. uncontrolled hypertension. ** $P < 0.05$ uncontrolled hypertension vs. untreated hypertension.

Figure 2. The absolute change from baseline in A) systolic blood pressure (SBP), B) diastolic blood pressure (DBP), C) mean arterial pressure (MAP) and D) heart rate (HR) during isometric handgrip exercise at 30% maximal voluntary contraction (0-30 and 30-60s handgrip (HG), post-exercise ischemia (PEI) (30 second ± periods PEI1, 2 and 3). * $P < 0.05$ for all groups vs. normotension. † $P < 0.05$ uncontrolled hypertension vs. normotension. ‡ $P < 0.05$ controlled hypertension vs. normotension.

Table 1. Participant Characteristics

	Normotension	Untreated Hypertension	Treated- uncontrolled hypertension	Treated- controlled hypertension
N	16	11	16	16
M/F	8/8	6/5	9/7	7/9
Age (Years)	65±1	65±2	66±2	67±1
Height (cm)	172±3	173±4	170±2	167±2
Weight (kg)	70±4	72±4	74±3	72±4
BMI (kg/m ²)	23.4±0.8	24.1±1	25.5±0.9	25.3±0.8
VO ₂ peak (ml/min/kg)	22.6±1.4	23.5±2.1	22.8±1.9	22.3±1.2
Daytime ABPM				
SBP (mmHg)	120±2	145±3*†	145±3*†	125±2
DBP (mmHg)	73±2	86±4*	86±2*†	77±2
MAP (mmHg)	89±2	106±3*†	105±2*†	93±1
HR (beats/min)	73±2	69±2	69±2	68±2
Clinic BP measurements				
SBP (mmHg)	126±2	148±5*	158±4*†	138±4
DBP (mmHg)	76±2	86±3*	89±2*†	80±2
MAP (mmHg)	93±1	106±3*	111±3*†	99±3
HR(beats/min)	69±3	67±3	64±3	65±3
Anti-Hypertensive Medications				

Median	N/A	N/A	1 (IQR=1-	2 (IQR=1-2)
number of			1.75)	
anti-				
hypertensive				
medications				

Percentage of participants taking anti-hypertensives (by class)				
ACEi (%)	0	0	44	88
ARB (%)	0	0	25	31
CCB (%)	0	0	44	56
α -blocker (%)	0	0	6	6
β -blocker (%)	0	0	6	6
Diuretics (%)	0	0	19	6

N; number, M; male, F; female, BMI; body mass index, VO₂ peak; peak volume of oxygen inspired, ABPM; ambulatory blood pressure monitoring, SBP; SBP, DBP; DBP, MAP, Heart rate; HR, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, CCB; calcium channel blocker, IQR; inter-quartile range. * $P < 0.05$ vs. normotension; † $P < 0.05$ vs. controlled hypertension (all one-way ANOVA with Tukey post-hoc test).